



NDA 19-591/S-014, S-017

Hoffman-LaRoche, Inc.
Attention: Lynn DeVenezia-Tobias
Program Manager, Drug Regulatory Affairs
340 Kingsland St.
Nutley, NJ 07110-1199

Dear Ms. DeVenezia-Tobias:

Please refer to your supplemental new drug applications dated August 19, 1999 and November 6, 2000, received August 24, 1999 and November 8, 2000, respectively, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lariam® (mefloquine hydrochloride) Tablets, 250 mg.

We acknowledge receipt of your submissions dated December 2, 2002 and December 19, 2002.

These supplemental new drug applications provide for the following changes to the Lariam® package insert. Added text is noted by double underline and deleted text is noted by ~~strikethrough~~:

1. CLINICAL PHARMACOLOGY

- A **Pharmacokinetic** subsection was added with subheadings to read:

~~Pharmacokinetic studies of mefloquine in healthy male subjects showed that a significant lagtime occurred after drug administration, and the terminal elimination half life varied widely (13 to 24 days) with a mean of about 3 weeks. Mefloquine is a mixture of enantiomeric molecules whose rates of release, absorption, transport, action, degradation and elimination may differ. A valid pharmacokinetic model may not exist in such a case.~~

~~Additional studies in European subjects showed slightly greater concentrations of drug for longer periods of time. The absorption half life was 0.36 to 2 hours, and the terminal elimination half life was 15 to 33 days. The primary metabolite was identified and its concentrations were found to surpass the concentrations of mefloquine.~~

~~Multiple dose kinetic studies confirmed the long elimination half lives previously observed. The mean metabolite to mefloquine ratio measured at steady state was found to range between 2.3 and 8.6.~~

~~The total clearance of the drug, which is essentially all hepatic, is approximately 30 mL/min. The volume of distribution, approximately 20 L/kg, indicates extensive distribution. The drug is highly~~

bound (98%) to plasma proteins and concentrated in blood erythrocytes, the target cells in malaria, at a relatively constant erythrocyte to plasma concentration ratio of about 2.

The pharmacokinetics of mefloquine in patients with compromised renal function and compromised hepatic function have not been studied. Pharmacokinetics

Absorption

The absolute oral bioavailability of mefloquine has not been determined since an intravenous formulation is not available. The bioavailability of the tablet formation compared with an oral solution was over 85%. The presence of food significantly enhances the rate and extent of absorption, leading to about a 40% increase in bioavailability. In healthy volunteers, plasma concentrations peak 6 to 24 hours (median, about 17 hours) after a single dose of Lariam. In a similar group of volunteers, maximum plasma concentrations in µg/L are roughly equivalent to the dose in milligrams (for example, a single 1000 mg dose produces a maximum concentration of about 1000 µg/L). In healthy volunteers, a dose of 250 mg once weekly, produces maximum steady-state plasma concentrations of 1000 to 2000 µg/L, which are reached after 7 to 10 weeks.

Distribution

In healthy adults, the apparent volume of distribution is approximately 20 L/kg, indicating extensive tissue distribution. Mefloquine may accumulate in parasitized erythrocytes. Experiments conducted in vitro with human blood using concentrations between 50 and 1000 mg/mL showed a relatively constant erythrocyte-to-plasma concentration ratio of about 2 to 1. The equilibrium reached in less than 30 minutes, was found to be reversible. Protein binding is about 98%.

Mefloquine crosses the placenta. Excretion into breast milk appears to be minimal (see **PRECAUTIONS: Nursing Mothers**).

Metabolism

Two metabolites have been identified in humans. The main metabolite, 2,8-bis-trifluoromethyl-4-quinoline carboxylic acid, is inactive in *P. falciparum*. In a study in healthy volunteers, the carboxylic acid metabolite appeared in plasma 2 to 4 hours after a single oral dose. Maximum plasma concentrations, which were about 50% higher than those of mefloquine, were reached after 2 weeks. Thereafter, plasma levels of the main metabolite and mefloquine declined at a similar rate. The area under the plasma concentration-time curve (AUC) of the main metabolite was 3 to 5 times larger than that of the parent drug. The other metabolite, an alcohol, was present in minute quantities only.

Elimination

In several studies in healthy adults, the mean elimination half-life of mefloquine varied between 2 and 4 weeks, with an average of about 3 weeks. Total clearance, which is essentially hepatic, is in the order of 30 mL/min. There is evidence that mefloquine is excreted mainly in the bile and feces. In volunteers, urinary excretion of unchanged mefloquine and its main metabolite under steady-state condition accounted for about 9% and 4% of the dose, respectively. Concentrations of other metabolites could not be measured in the urine.

Pharmacokinetics in Special Clinical Situations

Children and the Elderly

No relevant age-related changes have been observed in the pharmacokinetics of mefloquine. Therefore, the dosage for children has been extrapolated from the recommended adult dose.

No pharmacokinetic studies have been performed in patients with renal insufficiency since only a small proportion of the drug is eliminated renally. Mefloquine and its main metabolite are not appreciably removed by hemodialysis. No special chemoprophylactic dosage adjustments are indicated for dialysis patients to achieve concentrations in plasma similar to those in healthy persons.

Although clearance of mefloquine may increase in late pregnancy, in general, pregnancy has no clinically relevant effect on the pharmacokinetics of mefloquine.

The pharmacokinetics of mefloquine may be altered in acute malaria.

Pharmacokinetic differences have been observed between various ethnic populations. In practice, however, these are of minor importance compared with host immune status and sensitivity of the parasite.

During long-term prophylaxis (>2 years), the trough concentrations and the elimination half-life of mefloquine were similar to those obtained in the same population after 6 months of drug use, which is when they reached steady state.

In vitro and in vivo studies showed no hemolysis associated with glucose-6-phosphate dehydrogenase deficiency (see **ANIMAL TOXICOLOGY**).

- A **Microbiology** subsection was added with subheadings to read:

~~Microbiology: Strains of *Plasmodium falciparum* resistant to mefloquine have been reported.~~

Microbiology

Mechanism of Action

Mefloquine is an antimalarial agent which acts as a blood schizonticide. Its exact mechanism of action is not known.

Activity In Vitro and In Vivo

Mefloquine is active against the erythrocytic stages of *Plasmodium* species (see **INDICATIONS AND USAGE**). However, the drug has no effect against the exoerythrocytic (hepatic) stages of the parasite. Mefloquine is effective against malaria parasites resistant to chloroquine (see **INDICATIONS AND USAGE**).

Drug Resistance

Strains of *Plasmodium falciparum* with decreased susceptibility to mefloquine can be selected in vitro or in vivo. Resistance of *P. falciparum* to mefloquine has been reported, in areas of multi-

drug resistance in South East Asia. Increased incidences of resistance have also been reported in other parts of the world.

Cross Resistance

Cross-resistance between mefloquine and halofantrine and cross-resistance between mefloquine and quinine have been observed in some regions.

2. CONTRAINDICATIONS

The first sentence in this section was revised to read:

Use of Lariam is contraindicated in patients with a known hypersensitivity to mefloquine or related compounds (eg, quinine and quinidine) or to any of the excipients contained in the formulation.

3. PRECAUTIONS

- The first two paragraphs in the **General** subsection were revised to read::

General

Hypersensitivity reactions ranging from mild cutaneous events to anaphylaxis cannot be predicted.

General: In patients with epilepsy, Lariam may increase the risk of convulsions. The drug should therefore be prescribed only for curative treatment in such patients and only if there are compelling medical reasons for its use (see **PRECAUTIONS: Drug Interactions**).

Caution should be exercised with regard to activities requiring alertness and fine motor coordination such as driving, piloting aircraft, operating machinery, and deep-sea diving, as dizziness, a loss of balance, or other disorders of the central or peripheral nervous system have been reported during and following the use of Lariam. These effects may occur after therapy is discontinued due to the long half-life of the drug. Lariam should be used with caution in patients with psychiatric disturbances because mefloquine use has been associated with emotional disturbances (see **ADVERSE REACTIONS**).

- The fourth bullet in the **Information for Patients** subsection was revised to read:

- that when used as prophylaxis, the first dose of Lariam should be taken 1 week prior to ~~departure~~ arrival in an endemic area;

- The second paragraph in the **Drug Interactions** subsection was revised to read:

Because of the danger of a potentially fatal prolongation of the QTc interval, halofantrine ~~should~~ must not be given simultaneously with or subsequent to Lariam (see **WARNINGS**).

- The seventh paragraph in the **Drug Interactions** subsection was revised to read:

No other drug interactions are known. Nevertheless, the effects of Lariam on travelers receiving comedication, particularly ~~those on coagulants or antidiabetics~~ diabetics or patients using anticoagulants, should be checked before departure.

- The following statements were added to the end of the **Carcinogenesis, Mutagenesis, Impairment of Fertility** subsection, **Pregnancy, Teratogenic Effects** statement:

Women of childbearing potential should also be advised to practice contraception during malaria prophylaxis with Lariam and up to 3 months thereafter. However, in the case of unplanned pregnancy, malaria chemoprophylaxis with Lariam is not considered an indication for pregnancy termination.

- The following phrase was added to the first sentence in the **Carcinogenesis, Mutagenesis, Impairment of Fertility** subsection, **Nursing Mothers** statement:

Mefloquine is excreted in human milk in small amounts, the activity of which is unknown.

- A **Geriatric Use** subsection was added to the end of this section to read:

Geriatric Use

Clinical studies of Lariam did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. Since electrocardiographic abnormalities have been observed in individuals treated with Lariam (see **PRECAUTIONS**) and underlying cardiac disease is more prevalent in elderly than in younger patients, the benefits of Lariam therapy should be weighed against the possibility of adverse cardiac effects in elderly patients.

4. ADVERSE REACTIONS

- A subsection was added to the reference in the first sentence of the fourth paragraph to read:

Two serious adverse reactions were cardiopulmonary arrest in one patient shortly after ingesting a single prophylactic dose of mefloquine while concomitantly using propranolol (see **PRECAUTIONS: Drug Interactions**), and encephalopathy of unknown etiology during prophylactic mefloquine administration.

5. OVERDOSAGE

- This section was revised to read:

In cases of overdosage with Lariam, the symptoms mentioned under **ADVERSE REACTIONS** may be more pronounced. The following procedure is recommended in case of overdosage: Induce vomiting or perform gastric lavage, as appropriate. Monitor cardiac function (if possible by ECG) and neurologic and psychiatric status for at least 24 hours. Provide symptomatic and intensive supportive treatment as required, particularly for cardiovascular disturbances. ~~Treat vomiting or diarrhea with standard fluid therapy.~~

6. DOSAGE AND ADMINISTRATION (see INDICATIONS AND USAGE)

- The **Adult Patients** subsection was revised to read:

Treatment of mild to moderate malaria in adults caused by *P. vivax* or mefloquine-susceptible strains of *P. falciparum*

Five tablets (1250 mg) mefloquine hydrochloride to be given as a single oral dose. The drug should not be taken on an empty stomach and should be administered with at least 8 oz (240 mL) of water.

If a full-treatment course ~~has been administered without clinical cure, alternative treatment should be given~~ with Lariam does not lead to improvement within 48 to 72 hours, Lariam should not be used for retreatment. An alternative therapy should be used. Similarly, if previous prophylaxis with mefloquine has failed, Lariam should not be used for curative treatment.

Note: Patients with acute *P. vivax* malaria, treated with Lariam, are at high risk of relapse because Lariam does not eliminate exoerythrocytic (hepatic phase) parasites. To avoid relapse after initial treatment of the acute infection with Lariam, patients should subsequently be treated with an 8-aminoquinoline derivative (eg, primaquine).

Malaria Prophylaxis

One 250 mg Lariam tablet once weekly.

Prophylactic drug administration should begin 1 week before ~~departure to~~ arrival in an endemic area. Subsequent weekly doses should ~~always~~ be taken regularly, always on the same day of ~~the~~ each week, preferably after the main meal. To reduce the risk of malaria after leaving an endemic area, prophylaxis ~~should~~ must be continued for 4 additional weeks to ensure suppressive blood levels of the drug when merozoites emerge from the liver. Tablets should not be taken on an empty stomach and should be administered with at least 8 oz (240 mL) of water.

In certain cases, eg, when a traveler is taking other medication, it may be desirable to start prophylaxis 2 to 3 weeks prior to departure, in order to ensure that the combination of drugs is well tolerated (see PRECAUTIONS: Drug Interactions).

When prophylaxis with Lariam fails, physicians should carefully evaluate which antimalarial to use for therapy.

- The **Pediatric Patients** subsection was revised to read:

Treatment of mild to moderate malaria in pediatric patients caused by mefloquine-susceptible strains of *P. falciparum*

Twenty (20) to 25 mg/kg ~~for non-immune patients~~ body weight. Splitting the total ~~curative~~ therapeutic dose into 2 doses taken 6 to 8 hours apart may reduce the occurrence or severity of adverse effects. Experience with Lariam in infants less than 3 months old or weighing less than 5 kg is limited. The drug should not be taken on an empty stomach and should be administered with ample water. ~~For very young patients, the dose may be crushed, mixed with water or sugar water and may be administered via an oral syringe.~~

The tablets may be crushed and suspended in a small amount of water, milk or other beverage for administration to small children and other persons unable to swallow them whole.

~~If a full-treatment course has been administered without clinical cure, alternative treatment should be given~~ with Lariam does not lead to improvement within 48 to 72 hours, Lariam should not be used for retreatment. An alternative therapy should be used. Similarly, if previous prophylaxis with mefloquine has failed, Lariam should not be used for curative treatment.

In pediatric patients, the administration of Lariam for the treatment of malaria has been associated with early vomiting. In some cases, early vomiting has been cited as a possible cause of treatment failure (see **PRECAUTIONS**). If a significant loss of drug product is observed or suspected because of vomiting, a second full dose of Lariam should be administered to patients who vomit less than 30 minutes after receiving the drug. If vomiting occurs 30 to 60 minutes after a dose, an additional half-dose should be given. If vomiting recurs, the patient should be monitored closely and alternative malaria treatment considered if improvement is not observed within a reasonable period of time.

The safety and effectiveness of Lariam to treat malaria in pediatric patients below the age of 6 months have not been established.

Malaria Prophylaxis

The following doses have been extrapolated from the recommended adult dose. Neither the pharmacokinetics, nor the clinical efficacy of these doses have been determined in children owing to the difficulty of acquiring this information in pediatric subjects. The recommended prophylactic dose of Lariam is ~~3 to~~ approximately 5 mg/kg body weight once weekly. One 250 mg Lariam tablet should be taken once weekly in pediatric patients weighing over 45 kg. In pediatric patients weighing less than 45 kg, the weekly dose decreases in proportion to body weight:

30 to 45 kg:	$\frac{3}{4}$ tablet
20 to 30 kg:	$\frac{1}{2}$ tablet
up <u>10</u> to 20 kg:	$\frac{1}{4}$ tablet
<u>5 to 10 kg:</u>	<u>_____ tablet*</u>

*Approximate tablet fraction based on a dosage of 5 mg/kg body weight. Exact doses for children weighing less than 10 kg may best be prepared and dispensed by pharmacists.

Experience with Lariam in infants less than 3 months old or weighing less than 5 kg is limited.

7. HOW SUPPLIED

The last sentence in this section was revised to read:

Tablets should be stored at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F).

We have completed the review of these supplemental applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use

as recommended in the agreed upon labeling text. Accordingly, these supplemental applications are approved effective on the date of this letter:

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert).

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplements NDA 19-591/S-014, S-017." Approval of this submission by FDA is not required before the labeling is used.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Robin Anderson, Labeling Reviewer, at (301) 827-2127.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.
Director
Division of Special Pathogen and Immunologic Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

Renata Albrecht
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